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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/457,931	12/08/1999	H. RALPH SNODGRASS	441472000100	8228

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	26

DATE MAILED: 10/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/457,931	H. Ralph Snodgrass
Examiner	**Art Unit**
Shin-Lin Ch n	1633

-- The MAILING DATE of this communication appears on the cover she t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jul 24, 2002

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 2-23 and 25-41 is/are pending in the applica

4a) Of the above, claim(s) 19, 20, and 34-41 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 2-8, 10-18, 21-23, and 25-33 is/are rejected.

7) ☒ Claim(s) 9 is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 20 & 21
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment filed 7-24-02 has been entered. Claims 1 and 24 have been canceled. Claims 3, 7 and 21-23 have been amended. Claims 2-23 and 25-41 are pending and claims 2-18, 21-23 and 25-33 are under consideration.

Applicant's request for rejoinder of claims 5 and 6 is not understood by examiner. There is no election of species for claims 5 and 6, and claims 5 and 6 have been under consideration according to the prosecution history of the present application. Therefore, it is unclear why there is a request for rejoinder for claims 5 and 6.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 5, 11, 16, 26 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 depends on canceled claim 1. It is unclear what applicant intends to claim in claim 5.

The phrase "therapeutic agents" in claims 11 and 26 is vague and renders the claims indefinite. It is unclear as to the metes and bounds of what would be considered "therapeutic agents"? The specification fails to specifically define the phrase "therapeutic agents".

The phrase "animal therapeutics" in claims 16 and 31 is vague and renders the claims indefinite. It is unclear as to the metes and bounds of what would be considered "animal therapeutics"? The specification fails to specifically define the phrase "animal therapeutics".

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 2-8, 10-18, 21-23 and 25-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spielmann et al., 1997 (In Vitro Toxicology, Vol. 10, No. 1, p. 119-127) in view of Craig et al., 1996 (Biomarkers, Vol. 1, No. 2, p. 123-135 and Wobus et al., 1999 (US Patent 6,007,993).

Claims 2-8 and 10-18 are directed to a method of compiling a library of molecular profiles of chemical compositions having predetermined toxicities by comparing the expression of sets of genes or proteins in a mammalian embryoid body with or without treating the chemical composition and creating patterns of alterations in gene expression or protein expression and compiling a library of molecular profiles with at least two chemical compositions with predetermined toxicities. Claims 21-23 and 25-33 are directed to a method of typing toxicity of a test chemical composition by comparing the molecular profiles of gene or protein expression in

an isolated mammalian embryoid body (EB) with or without the treatment of said test chemical composition, and a method of typing toxicity or ranking toxicity of a test chemical composition by comparing the molecular profiles of gene or protein expression in an isolated mammalian embryoid body (EB) having the treatment of said test chemical composition with a composite library of molecular profiles of chemical compositions having predetermined toxicities. Claims 26-28 and 31-33 specify the chemical composition having predetermined toxicities are therapeutic agents, neurotoxins, renal toxins, hepatic toxins, myotoxins, agents that are toxic to cells of one or more reproductive organs, teratogenic agents, carcinogens, agricultural chemicals, cosmetics, or environmental contaminants.

Spielmann teaches a method of using mouse embryonic stem cells *in vitro* for embryotoxicity testing comprising culturing the embryonic stem cells to a stage where the cells form embryoid bodies, contacting the bodies with a variety of chemical compositions, and determining the cytotoxicity of the chemical compositions by MTT cytotoxicity assay. Spielmann uses 16 test chemicals which are assigned to three classes of *in vivo* embryotoxicity and compiles libraries of the "molecular profiles" of the test chemicals and ranks the chemical compositions with respect to their relative toxicities (e.g. abstract, p. 120, 121, Figure 1, Table 1).

Spielmann does not teach creating the molecular profiles of gene expression or protein expression.

Craig teaches using embryos of the topminnow, *Fundulus heteroclitus*, for reproductive toxicity screening by exposing the embryos to teratogenic concentrations of sodium valproate (VPA) or arsenic acid (arsenate) and evaluating the frequency and types of induced malformations. Craig correlates the teratogenic outcomes to specific alterations in the expression of a panel of developmentally regulated genes and the genetic expression profiles revealed a number of genes whose expression levels were significantly altered by exposure to the test compounds (e.g. abstract). Craig also teaches generating cDNA from mRNA and using ^{32}P-labeled probes for the detection of gene expression in establishing gene expression profiles (e.g. p. 125, left column).

Wobus teaches an in vitro test procedure for detecting chemically-induced embryotoxic/teratogenic effects based on differentiated pluripotent embryonic stem cells or embryonic germ cells obtained from primordial germ cells of the mouse or rat. A differentiation-dependent expression of tissue-specific genes of embryonic stem cell clones or embryonic germ cell clones is furnished in the presence of teratogenic substances. The substances act at specific times of the in vitro differentiation and subsequent differentiation. A chemically-induced activation, repression or modulation of the tissue-specific genes which influence embryonic development is detected (e.g. column 2, lines 53-67). The cell clones contain reporter gene constructs which can be specifically activated, repressed or modulated in the course of the differentiation by exogenic test substances, such as retinoic acid, and the differentiation-dependent expression during the test procedure can be carried out by embryoid body

differentiation in different lines (e.g. column 3, lines 1-23). The reporter gene can be LacZ or the luciferase gene and detection can be by a simple staining reaction (e.g. column 3, lines 53-63). Promoters of the reporter gene constructs can be neuronal, cardiogenic, muscle and skeletal specific to monitor development (e.g. column 4, lines 2-14) in the presence of the exogenic test substance. Wobus teaches recording alterations in gene expression by monitoring protein expression after contacting an embryoid body with a chemical composition, and the change in expression is detected by a colorimetric label, e.g. X-Gal staining (e.g. column 4, 7).

It would have been obvious for one of ordinary skill at the time of the invention to substitute the MTT cytotoxicity assay as taught by Spielmann with detection of gene expression as taught by Craig or detection of protein expression as taught by Wobus because it was known in the art to determine the effect of a chemical compound by detecting the alteration of gene expression or alteration of protein expression.

One ordinary skill in the art at the time the invention was made would have been motivated to do so in order to generate a gene expression profile or protein expression profile of a teratogenic agent by using embryos or embryoid bodies as compared to a control having no treatment of said teratogenic agent as taught by Craig and Wobus, respectively, or to generate a library of gene expression or protein expression profiles of a test composition for typing or ranking toxicity of said test composition by using embryos or embryoid bodies according to the collective teachings of Spielmann, Craig, and Wobus with reasonable expectation of success.

Conclusion

Claims 2-8, 10-18, 21-23 and 25-33 are rejected. Claim 9 is objected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.